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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,438	06/25/2007	Raymond Nadeson	210174.401USPC	9722

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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1619	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,438	NADESON ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 12, 2010 has been entered.

Claims 43-50 are pending in this application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 43-45, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999 15-20)

Nickel et al. teach that flupirtine is a centrally acting analgesic (see introduction) and teach administration of flupirtine in combination with morphine for treatment of pain wherein it was demonstrated that the combination provided an increase in analgesic activity and furthermore flupirtine weakens morphine induced tolerance, physical dependence and behavior changes (see methods/results). It further states that flupirtine enhances the analgesic effects of opioids and this is confirmed in studies on cancer patients (see discussion).

Nickel et al. does not teach specifically treatment of neuropathic pain.

Grond et al. teach that neuropathic pain syndromes are one of the major problems of cancer pain treatment. Grond et al. teach employing an opioid analgesic

(such as morphine) and non-opioid analgesics for the treatment of neuropathic pain stemming from cancer (see abstract and see table 1).

Grond et al. does not teach administration of flupirtine.

It would have been obvious to employ the combination of flupirtine and an opioid analgesic, such as morphine for the treatment of neuropathic pain, especially from cancer pain, motivated by the teaching of Nickel et al. who teach that flupirtine is a centrally acting analgesic (see introduction) that enhances the analgesic effects of opioids, such as morphine for treatment of cancer pain, and the teaching of Grond et al. who teach that neuropathic pain syndromes are one of the major problems of cancer pain treatment and teach that opioids are often combined with non-opioid agents in the treatment of cancer pain.

Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999) as applied to claims 43-45, 48 and 49 above, and further in view of Perovic et al (Neurodegeneration, Vol. 4 pages 369-374 (1995)).

Perovic et al. teach that flupirtine is a clinically safe compound with drowsiness reported in only 10% of cases (page 373, column 2). Since the dosage of the opioid is not disclosed, then the claim encompasses an almost negligible amount of opioid and as such overt sedation would not occur since it is dose related.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ a non sedating combination of flupirtine and an opioid motivated by the

teaching of Perovic et al. that flupirtine caused drowsiness in only 10 % of cases combined with the well known fact that sedation of opioid analgesics is dose related and since the claims do not disclose the dosage, they encompass a negligible amount of opioid. Further, Nickel et al. teach that flupirtine weakens morphine induced behavior changes (see methods/results). One having ordinary skill in the art at the time the invention was made would reasonably deduce that sedation is one of the primary behavior changes that morphine induces.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999) as applied to claims 43-45, 48 and 49 above, and further in view of Devulder at al. (U).

Devulder et al. teach the dose of flupirtine for treatment of neuropathic (central) pain is 300-600 mg/day. The instant claim is drawn to 0.5mg/kg to about 20 mg/kg of body weight. Translating the dose of Devulder et al. to mg/kg based on an average 80 kg human the dosage would be 3.75 mg/kg[1] to 7.5 mg/kg[2]. This dosage amount is encompassed by the claimed amount of 0.5 mg/kg to about 20 mg/kg. A prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." *In re Peterson*, 315 F.3d

[1] 300 mg / 80 kg = 3.75 mg/kg
[2] 600 mg / 80 kg = 7.5 mg/kg

1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005).

It would have been made obvious to one of ordinary skill in art at the time it was made to employ 0.5 mg/kg to about 20 mg/kg of flupirtine in the composition combined with another opioid agent, such as morphine to treat neuropathic pain motivated by the teaching of Nickel et al. and Grond et al supra.and the teaching of Devulder et al. who teaches that the dosage of flupirtine for central (neuropathic) pain is 300 to 600 mg/day (approximately 3.75 mg/kg to about 7.5 mg/kg).

Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999) as applied to claims 43-45, 48 and 49 above, and further in view of Cleary (Cancer Control, 2000).

Cleary teaches that cancer pain can have a neuropathic component (page 122, column 2 “character”). It further identifies specific cancers for which such neuropathies occur, such as colon cancer, non-small cell lung cancer and multi-organ system failure associated with cancer (page 121, column 2 bridging to page 122). Cleary also discloses that although opioids are the mainstay of cancer pain management, adjunct therapy is recommended. Adjuvant medications may result in a decrease in opioid dose with an associated decrease in side effects and adjuvant therapy is often useful with opioids in the treatment of neuropathic pain. (page 127, column 2).

Response to Arguments

Applicant's arguments with respect to claims 43-50 have been considered but are moot in view of the new ground(s) of rejection.

Applicant states that synergism is observed when combining flupirtine with an opioid analgesic. The examiner encourages Applicant to submit the Declaration that is explained in the remarks for consideration. However, with regard to synergy, The MPEP states that a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.) (MPEP § 716.02(a)).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

Donna Jagoe /D. J./
Examiner
Art Unit 1619

May 6, 2010